Role of Pregabalin in Management of Pruritus: A Literature Review

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ABSTRACT - Purpose. Pruritus can be one of the distressing symptoms of many dermatologic, systemic, neurologic or psychiatric disorders. In each case, the origin of itch is in the skin and/or the nervous system. Involvement of the nervous system causes neurogenic, psychogenic or neuropathic itch. Itch sensation is transferred to the central nervous system via unmyelinated C-type nerve fibers, and many mediators and receptors engage in the its induction and transmission. Also it has been demonstrated that there are similarities and interactions between neurotransmitters and pathways of pain and itch sensation. Hence, effective drugs in reducing the neuropathic pain such as pregabalin have been studied and used in the management of different itchy conditions. In this narrative review we considered the available published papers dealing with the antipruritic effects of pregabalin. Results of studies conducted in uremic patients show that pregabalin is an effective option in reducing uremic pruritus especially in those who have not responded to antihistamines and topical moisturizers. Data about the effects of pregabalin on other itchy conditions are very limited; however results of the available studies show beneficial effects of this drug in burn patients with more than 5% involvement of the total body surface area, in prurigo nodularis, and in chronic and idiopathic itch. One considerable issue is that the therapeutic effects of pregabalin on uremic pruritus and post burn itch may appear more rapidly than its effects in the other conditions (1-2 weeks vs > 4 weeks). The most reported adverse effects of pregabalin are sedation, dizziness and drowsiness. Whether pregablin can be unequivocally considered as an effective and reasonable choice in the management of pruritus with different causes is a question that should be answered through large scale randomized controlled studies.

INTRODUCTION

Pruritus is a cutaneous sensation that causes the tendency to scratch the skin. It can be a physiologic response against harmful agents such as parasites or a symptom of a disease (1, 2). Many skin and systemic diseases such as renal insufficiency, cholestasis, Hodgkin's lymphoma, polycythemia vera, and solid tumors cause pruritus that in most cases required drug therapy (2-4).

Pruritus is classified based on its origin or its chronicity. Regarding the origin, pruritus is divided into 2 classes, peripheral and central. Peripheral itch arises from the skin or damaged nervous system (neuropathic itch), but central itch arises from either the damaged nervous system (neuropathic itch) or the healthy central nervous system (CNS) (neurogenic itch). Moreover, some psychiatric disorders can cause pruritus (psychogenic itch) (5). Considering chronicity, duration of pruritus is a criterion for its classification. In this manner a 6 week duration is the boundary between an acute and a chronic itch (6).

It is worth mentioning that not only is chronic itch a bothersome sensation by itself, but it also is a negative factor that can reduce quality of life. Pruritus affects different physical, social and psychological aspects of the life. It can cause sleep disturbances, agitation, and anxiety and can reduce concentration, sexual desire and sexual function (1, 3, 7-9). Therefore, treatment of pruritus is an

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important point in the management of many skin and systemic diseases. Surely treatment of underlying disease relieves pruritus, but many diseases have no cure and progress over time which necessitates choosing strategies for symptomatic treatment of itch (4).

Antipruritic medications affect transmission of the itch sensation in the central or peripheral nervous system. Drugs such as antihistamines, menthol, capsaicin, topical calcinurin inhibitors, cannabinoid agonists and leukotriene antagonists act peripherally while medications such as antidepressants, antagonists of mu-opioid receptor and antiepileptics such as gabapentin and pregabalin act centrally (2).

Pregabalin is an analogue of the gamma amino butyric acid (GABA) that binds to the voltage gated calcium channels. Pregabalin reduces effects of substance P and release of several excitatory neurotransmitters and calcitonin gene related peptide. It has been hypothesized that these effects on different neurotransmitters and peptides are responsible for the broad therapeutic effects of pregabalin such as reducing neuropathic pain and anxiety and controlling epilepsy (10).

Exact mechanism of action of pregabalin in reducing the itch sensation is not clear (11, 12). In a mouse model of oxazolone induced chronic atopic dermatitis, treatment with pregabalin and gabapentin decreased scratching behaviors, and authors of this study suggested that the antipruritic effects of these drugs may be because of the binding to the α2δ subunit of the voltage-gated calcium channels in the dorsal root ganglion of the spinal cord (13).

Although different sensory neurons and pathways mediate the sensation of pain and itch, there are some common mediators and receptors in the both systems (13-15). Because of these similarities it has been suggested that drugs such as pregabalin which is an effective medication in the reduction of the neuropathic pains (2, 16-20) may have potential benefits in decreasing the itch severity, especially the neuropathic one. Consequently, we tried to review the available published studies that investigated antipruritic effects of pregabalin. Based on our knowledge it is the first narrative review in this domain.

METHODS

We searched PubMed, Google Scholar, Scopus and Science Direct Databases using key words “pregabalin”, “itch”, and “pruritus”. This search was done with any time limitation. All available published articles were included. A summary of the characteristics of the reviewed reports is presented in Table 1.

Table 1. Summary of characteristics of published articles about antipruritic effects of pregabalin

Author	Cause of itch	Intervention	Number of patients	Severity of pruritus at baseline*	Duration of treatment	Results
Aperis et al (26)	Uremia (in HD patients)	Pregabalin 25 mg/day	16	Moderate	1 month	Significant improvement of pruritus and reduction in the score of the VAS
Guru et al (27)	Uremia (in HD patients)	Pregabalin 75 mg every other day	20	Severe	4 weeks	Significant reduction in the score of the VAS
Solak et al (28)	Uremia (in HD patients)	Pregabalin 75 mg/day vs. gabapentine 300 mg thrice weekly	29	Moderate	6 weeks	Both drugs significantly and to the same degree reduced the score of the VAS.
Shavit et al (29)	Uremia (in CKD patients)	Pregabalin Initial dose: 25 mg 3 times/week	12	Severe	24 weeks	Significant improvement after one week of the treatment, and this effect continued to the 24th week of the treatment

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Author	Cause of itch	Intervention	Number of patients	Severity of pruritus at baseline*	Duration of treatment	Results
Rayner et al (30)	Uremia (in CKD and HD and PD patients)	Pregabalin Initial dose:25 mg every other day in HD patients and 25 mg daily in CKD and PD patients	16	Moderate to severe	2.5 months	Significant improvement
Yue et al (31)	Uremia (in HD and PD patients)	Pregabalin (75 mg 2 times/week in PD patients and 75 mg 3times/week in HD patients) vs. Ondansetron vs. Placebo	179	Moderate to severe	12 weeks	Significant improvement was only observed in the pregabalin group
Foroutan et al (32)	Uremia (in HD patients)	Pregabalin 50 mg 3 times/week vs. Doxepin 10 mg/day	72	Moderate to very severe	4 weeks	Pregabalin was significantly more effective than doxepin in reducing the severity of itch and improving the quality of life,
Ahuja et al (40)	Post burn itch	P (different doses based on the severity of the pruritus) vs. P+Ph+C vs. Ph+C vs. Pl	80	Moderate	28 days	P and P+Ph+C were more effective than the other interventions
Gray et al (41)	Post burn itch	Pregabalin Initial dose: 75 mg BID	90	Score of NPS- 7 at baseline was:2-3	4 weeks	Pregabalin Significantly reduced the score of the NPS-7 in comparison with placebo
Mazza et al (50)	PN	Pregabalin 75 mg/day	30	severe	3 months	significant improvement
Imai et al (51)	PN	Pregabalin Initial dose: 150 mg/day	1	Severe	50 weeks	Significant improvement after 1 day of the treatment
Porzio et al (49)	Cetuximab-based chemotherapy	Pregabalin Initial dose: 75 mg BID	1	Severe	Until chemo-therapy courses were continued	Significant improvement
Park et al (48)	Chronic itch without any systemic or skin diseases	Pregabalin 75 mg BID	22	Moderate	8 weeks	Significant improvement
Ehrchen et al (15)	Unknown cause in 1 patient and aquagenic pruritus due to polycythemia vera in 2 patients	Pregabalin Initial dose: 75 BID	3	Moderate	5-8 weeks	More than 70% reduction in the itch intensity

*: VAS scores of 2-5, 6-8 and 9-10 were assumed to be representative of mild, moderate and severe pruritus, respectively.(41, 42)
BID: two times per day; C: Cetirizine; CKD: Chronic Kidney Disease; HD: Hemodialysis; NRS: Numerical Rating Scale; P: Pregabalin; PD: Peritoneal Dialysis; Ph: Pheniramine maleate; Pl: Placebo; PN: Prurigo Nodularis; VAS: Visual Analogue Scale

RESULTS

Antipruritic Effects of Pregabalin on Uremic Pruritus

More than 50% of patients with end stage renal disease (ESRD) complain of pruritus (21-23). The most commonly used agents in the management of uremic pruritus are antihistamines, topical moisturizers and corticosteroids which are not satisfactorily effective in all patients (24). Since one of the proposed etiologies of uremic pruritus is peripheral neuropathy, drugs such as pregabalin may be effective in reducing this type of pruritus (21, 25).

Aperis et al. evaluated the effects of pregabalin in 16 hemodialysis patients aged 37-80 years who were suffering from uremic pruritus, the problem that had not responded to antihistamines. The dose of pregabalin was 25 mg daily. Twelve patients completed the study, and results showed that pregabalin significantly reduced the mean score of visual analogue scale (from 7.44 ± 2.01 at baseline to 1.7 ± 1.31 after one month of the treatment, $p < 0.001$). They noted that 4 patients left the study due to the adverse effects which were dizziness and somnolence in 3 participants and blurred vision and hand tremor in the other one (26).

Guru et al. conducted a non-randomized single arm study in 20 hemodialysis patients whose average age was 57.05 ± 7.52 years. All included patients had severe uremic pruritus resistant to emollients, antihistamines, xylocaine cream and tacrolimus ointment. Prescribing 75 mg of pregabalin every other day for 4 weeks significantly reduced the mean score of the visual analog scale (from 7.72 ± 0.93 at baseline to 5.94 ± 0.36 at the end of the study, $p<0.0001$). The reported adverse effects were drowsiness, vertigo, sedation and ataxia (27).

With the aim of comparing efficacy of pregabalin with gabapentin in the management of uremic pruritus and neuropathic pain, Solak et al. entered 50 hemodialysis patients suffering from neuropathy and/or neuropathic pain in a 14 week cross over open label randomized study. Twenty nine of the included patients also had pruritus. Patients were randomly assigned to receive 75 mg of pregabalin per day or 300 mg of gabapentin after each hemodialysis session for 6 weeks, and after a 2 week washout period their treatment regimen was changed to the other drug for another 6 week period. The baseline average score of the visual analog scale in patients with pruritus was 5.84 ± 1.38, and after 6 weeks of the treatment, both gabapentin and pregabalin significantly reduced the average score of the visual analog scale to 1.43 ± 2 and 1.36 ± 2.32, respectively. However, the difference between the two drugs was not significant ($p=0.844$). The most reported adverse effects of both drugs were dizziness and somnolence (28).

In a 24 week trial, Shavit et al. studied the effects of pregabalin on uremic pruritus (UP) in 10 hemodialysis patients and 2 patients with chronic kidney disease stage 4 (average age: 72 ± 9 years) who had not responded satisfactorily to antihistamines and topical moisturizers. The initial dose of pregabalin was 25 mg three times per week, and the dose could be increased to 25 mg per day and 50 mg per day in non-responders. The mean score of the visual analog scale (VAS) at baseline was 9.7± 0.9. More than 60% of the participants showed a rapid and effective response while others showed a clinical improvement after 4 weeks, and the therapeutic response continued to the twenty fourth week of the treatment in all patients. The mean scores of the VAS at the end of the first, the fourth and the twenty fourth weeks of the treatment were 3.7 ± 2.35, 3.2 ± 1.75 and 3 ± 1.5, respectively. Beside these therapeutic effects, two patients reported somnolence and dizziness as the adverse effects (29).

Rayner et al. studied the effects of gabapentin on 71 patients out of whom 25 were in the stage 4 or 5 of chronic kidney disease and 46 were on dialysis. The participants were suffering from moderate to severe pruritus, and 63% of them had not responded to antihistamines. In this study, 16 out of the 21 patients who stopped gabapentin due to bothersome side effects were treated with pregabalin. The initial dose of pregabalin was 25 mg daily in chronic kidney disease and peritoneal dialysis patients and 25 mg after each dialysis session in hemodialysis patients, and according to patients' response the doses were titrated upward. Pregabalin alleviated pruritus in 81% of the patients after a median time of 2.5 months (the median severity of itch reduced from 8 to 2). Over sedation was the sole reported adverse effect of pregabalin which occurred in 2 patients (30).

Yue et al. conducted a triple arm study to

compare the antipruritic effects of pregabalin with ondansetron and placebo in 179 dialysis patients aged more than 16 years. The dose of pregabalin was 75 mg twice per week in peritoneal dialysis patients and 75 mg after each dialysis session in hemodialysis patients. The dose of ondansetron was 8 mg daily. The VAS and modified Duo's VAG Scale were used to evaluate the severity of itch. The quality of sleep, and the health related quality of life were evaluated by Pittsburgh sleep quality index and the Chinese version of the 12-item short-form (SF-12) general health survey, respectively. After 12 weeks of the treatment, only pregabalin significantly reduced the mean score of the VAS and the modified Duo's VAG Scale and significantly improved the quality of sleep and the health related quality of life. The effects of ondansetron on all of the above mentioned domains were similar to the placebo effects (31).

Results of a 4 week study designed by Foroutan et al. showed that pregabalin (50 mg after each dialysis session) was more effective than doxepin (10 mg/day) in reducing the severity of UP, evaluated by the VAS and 5-D itch scale, and improving quality of life, evaluated by the 5-D itch scale and dermatology life quality index, in a group of hemodialysis patients (N= 72). They also noted that the most antipruritic effects of pregabalin appeared at the end of the first week of the study, and the effects continued through the remained course of the trial. The mean scores of the VAS at baseline were 7.5 ± 1.4 and 7.1 ± 1.3, and at the end of the study were reduced to 2.1± 2.6 and 4.2 ± 2.6 in the pregabalin and doxepin group, respectively (32).

Collectively results of the above mentioned studies suggest that pregabalin can be an effective medication in the management of UP especially in patients who do not respond to the antihistamines. However, a wide range of doses of pregabalin has been used in these studies; therefore, designing studies for finding the most appropriate dose of pregabalin in this patient population is necessary.

Antipruritic Effects of Pregabalin on the Post Burn Itch

Healing wounds and healed wounds of burn even those treated with the skin graft often cause pruritus in burned patients. Although the predominant origin of the pruritus in burn cases is the skin, the neuropathic mechanisms may also be involved. The most commonly used drugs to reduce the post burn itch, are antihistamines. Unfortunately, these drugs have not impressive therapeutic effects on all patients (33, 34); therefore, researchers have studied the antipruritic effects of the other drugs such as local anesthetics (35), naltrexon (36), gabapentin (37-39), and pregabalin in the management of post burn pruritus.

Ahuja et al. in a four arm, double blind, randomized controlled trial (RCT) assigned 80 patients afflicted by post burn pruritus to four groups which were cetirizine plus pheniramine maleat (group A), pregabalin plus cetirizine plus pheniramine maleat (group B), placebo (vitamin B-complex) (group C) and pregabalin (group D). The inclusion criteria were having the second degree burns with more than 5% of the total body surface area (TBSA) involvement and having wounds in the healing phase (80% epithelialized) or wounds healed in the last 3 months before entering to the study. The mean score of the VAS was between 6 and 8 at the baseline. After 28 days of the treatment the percentage of decrease in the itch severity in the B and D groups were significantly more than that of the A and C groups. Collectively, the results of this study show that pregablin alone or in combination with antihistamines can completely (in mild-moderate itch) or near completely (in sever itch) relieve post burn itch. Furthermore, combination of pregabalin with antihistamine drugs had no more therapeutic effects than those of pregabalin alone, yet the sedative effect of this combination was more than that of each drug in isolation (40).

Effects of pregabalin on post burn pain were evaluated in a randomized double blind placebo controlled trial. Ninety patients aged 18-65 years whose total body surface area involvement was more than 5% were included. Pregabalin was started at 75 mg twice per day, and the dose could be increased to 300 mg twice per day based on the daily response of the patients. One of the secondary outcomes of this study was changes in the score of the seventh item of the NPS (NPS 7) which is "itch". After 28 days, the patients in the pregabalin group showed significant reduction in the score of this item compared to those in the placebo group. This improvement appeared at the second week and progressively continued to the end of the fourth week. Moreover, the most remarkable reduction in the itch severity was seen in the patients with more involvement of the total body surface area. It is

noteworthy that the adverse effects such as nausea, vomiting, drowsiness and giddiness occurred in similar rates in both groups, and drowsiness was also the most severe adverse effect (41).

Shortage of data about therapeutic effects of pregabalin on post burn itch makes conclusion very difficult; however, results of two reviewed studies show that pregabalin may be a promising drug in the management of post burn pruritus at least in the patients who have more than 5% of the total body surface area involvement. Surely, more studies in this domain are needed for more decisive conclusions.

Antipruritic Effects of Pregabalin on Prurigo Nodularis

Prurigo Nodularis (PN) is a severe papulonodualr pruritic skin condition that presents in different systemic diseases. The underlying pathogenesis of prurigo nodularis is not exactly known. It is observed that hypertrophy and proliferation of dermal nerves and an increase in the calcitonin gene related peptide (CGRP) and substance P immunoreactive nerves are typical neurologic changes in prurigo nodularis.

Prurigo Nodularis is a hard to treat condition. Some non-pharmacologic and many pharmacologic therapies such as UV light exposure, cryotherapy, laser beam, topical phenol, menthol cream, oral antihistamines, topical glucocorticoids, oral antidepressants, topical vitamin D3, capsaicin, cyclosporine, thalidomide, and naltrexone have been used in its management (42); however they often fail to control the pruritus effectively. Therefore, researches to find more effective therapeutic options are continuing, and case reports of using new medications such as methotrexate (43), Selective Serotonin Reuptake Inhibitors (44), butorphanol (45), gabapentin (46, 47) and pregabalin with some successful results are increasing in the literature. The inhibition of release of calcitonin gene related peptide by pregabalin may be one reason of its beneficial effects in the management of prurigo nodularis (48, 49).

Effects of pregabalin on PN were evaluated in an open label uncontrolled trial. Mazza et al. involved 30 patients, aged 37-66 years, who had not satisfactorily responded to previous medications. After 3 months of receiving pregabalin 75 mg/day, 76% of the patients showed complete remission defined as “disappearance of the pruritus and reduction of nodules”, and 20% slightly responded defined as “slight improvement/reduction of the nodules, that is, number and/or flattening, no disappearance of itching”. Besides, the average score of the VAS was 8.15 ± 2.04 at baseline and were reduced to 1.5 ± 1.12 after 3 months ($P < 0.0001$). Six patients experienced side effects that were sedation, dizziness, and headache (50).

Imai et al. reported a case of severe pruritus due to PN in a 78-year- old diabetic man who scratched his skin frequently which caused bleeding and cellulitis and osteomyelitis. After the unsuccessful courses of treatment with topical clobatasol and oral antihistamines, the treatment team decided to begin pregabalin at 150 mg/day. They evaluated itch severity using the VAS and 5-D itch scale and its impacts on the quality of life using the 5-D itch scale and the dermatology life quality index. After 1 day of the treatment, the patient experienced a dramatic improvement, and the score of the VAS were reduced by 8 units. At discharge, the dose of pregbalin was increased to 225 mg/day which caused more reduction in the severity of the itch, and this effect continued for 50 weeks after the introduction of pregabalin. It is worth mentioning that treatment with pregabalin reduced the score of the dermatology life quality index from 15 at baseline to 3, 2 and 1 at the end of the second, the fourth and the fiftieth weeks of the treatment, respectively. Furthermore, the score of the 5-D itch scale decreased from 22 at baseline to 10, 8 and 7 after 2, 4 and 50 weeks of the treatment, respectively (51).

In conclusion, nerve involvement and increase in calcitonin gene related peptide as one of the likely underlying causes of PN make pregabalin a good theoretical option for reducing itch in this condition, but this theory must be tested in high quality clinical studies. Although decision making based on the available low quality evidences about the beneficial effects of pregabalin in the management of pruritus caused by PN is not scientific, the results are promising, and these data can be a good reason for researchers interested in this topic to design large scale randomized clinical trials.

Antipruritic Effects of Pregabalin in Other Situations

Cetuximab induced severe itch in a 62-year-old man who suffered from a primary intestinal type

adenocarcinoma of the nasal cavity was reported by Porzio et al. Fifteen days after the first course of the cetuximab-based chemotherapy regimen, the patient experienced cutaneous adverse effects of cetuximab which were skin xerosis, acneiform lesions and intense pruritus. The severity of the pruritus was scored 9 -10 on a numerical rating scale. These side effects caused depression, sleep deprivation, anxiety and asthenia in the patient. Treatment of the pruritus with promethazine and a topical anti-inflammatory drug was ineffective. Therefore, chemotherapy was stopped, and pregabalin at dose of 75 mg twice a day was initiated, and the dose was increased to 100 mg twice a day at the third day. After significant reduction in the itch severity, depression, anxiety and asthenia by pregabalin, the clinicians restarted the chemotherapy regimen. Discontinuation of pregabalin caused prompt recurrence of severe pruritus which was reduced by resumption of pregabalin. The only reported adverse effect of pregabalin in this case was drowsiness (49).

In an open-label uncontrolled study, Park et al. evaluated the effects of pregabalin on chronic pruritus in 22 patients, aged 42-69 years, who did not have any special systemic or cutaneous diseases. The patients were not permitted to use corticosteroids and antihistamines for 4 weeks and 1 week before entrance to the study, respectively. Pregabalin was administered at 75 mg two times per day. After 4 weeks of the therapy the average score of the VAS was decreased significantly (from 6.95 at baseline to 4.68) ($P < 0.05$). It was also noted that 36.8 % of the patients were highly satisfied with the treatment, but 31.8% declared no improvement. The reported side effects of pregabalin were constipation, vertigo and heartburn (48).

Ehrchen et al. reported 3 cases with a 15-25 year history of generalized severe itch. Pruritus in one patient had no identifiable cause while aquagenic pruritus related to polycythemia vera was the cause of itch in the others. The patients had not responded satisfactorily to multiple therapeutic interventions; therefore, pregabalin was initiated at 75 mg twice per day, and subsequently the dose was increased to 150 mg twice per day. Receiving pregabalin for 5 to 8 weeks reduced the itch intensity by more than 70%, and its therapeutic effect continued during the 6 months of the follow up (15).

DISCUSSION

In general, this literature review demonstrates that pregabalin has been considered as an antipruritic medication in different conditions, i.e. post burn itch, UP, pruritus caused by prurigo nodularis, cetuximab induced itch, and chronic itch with indistinctive causes. Although these reviewed conditions do not have exactly similar pathogenesis, UP, post burn itch and prurigo nodularis induced itch have at least nerve involvement as the common underlying cause. As a result, the beneficial therapeutic effects of pregabalin in the management of neuropathic disorders make it a likely good option in the management of the neuropathic pruritus.

Pregabalin significantly reduces the severity of itch in all studies conducted in uremic patients. However, most of these studies were uncontrolled and open label and recruited a limited number of patients. Therefore, large scale controlled clinical trials are required to confirm the therapeutic role of pregabalin in these patients.

The results of the other studies included in our review show that pregabalin has acceptable antipruritic effects in the burn patients who have more than 5% of the total body surface area involvement, the patients suffering from prurigo nodularis and in the idiopathic chronic pruritus. Moreover, there are 5 case reports that are worthing consideration, one case of pruritus due to prurigo nodularis, three cases of the prolonged sever generalized itch, and one case of the cetuximab induced itch. Prescription of pregabalin significantly reduced the severity of pruritus in all of these cases.

In conclusion, only a limited number of studies have evaluated the antipruritic effects of pregabalin in different itchy conditions. They typically suggest beneficial effects; however, most of these studies are non- randomized open label and single arm with small sample sizes and used a wide range of doses of pregabalin. This makes clinical decision on appropriate dose of pregabalin difficult. Hence, to confirm the efficacy of pregabalin in the management of pruritus well designed clinical studies are needed.

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